IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: Curatolo et al.

SERIAL NO.: 09/918,127

FILED: July 30, 2001

FOR: Pharmaceutical Compositions Of Cholesteryl Ester Transfer Protein Inhibitors

Examiner: Fubara, Blessing M.
Art Unit: 1615

Commissioner for Patents
Washington, D.C. 20231

Sir:

DECLARATION UNDER 37 CFR 1.132

I, Dwayne T. Friesen, declare that:

1. I was awarded the degree of Ph.D. in Physical Chemistry, Oregon State University, Corvallis, Oregon, 1980 and a degree of B.S. in Chemistry, California State College, Bakersfield, California, 1975.

2. I have been employed by Bend Research, Inc., since 1980. My title is Vice President, Research. I am a director and part owner of Bend Research, Inc.

3. Bend Research, Inc. is part owned by Pfizer, Inc., the Assignee of the above-identified application.

4. I am one of the inventors of the instant patent application. I have read the Office Action, which was mailed April 20, 2004.

5. The inventions claimed in the present patent application are pharmaceutical compositions comprising a solid amorphous dispersion. The solid amorphous dispersion comprises a cholesteryl ester transfer protein (CETP) inhibitor and a concentration-enhancing polymer. Sikorski (WO 99/14204) does not disclose the use of a solid amorphous dispersion. Rather, Sikorski, in discussing the use of adjuvants for administration of a CETP inhibitor, states "Such capsules or tablets may contain a controlled-release formulation as may be provided in a dispersion of active compound in hydroxypropylmethyl cellulose." (Page 84). Sikorski, therefore, uses the term "dispersion" to mean a controlled release matrix in which drug particles are distributed within a polymer matrix that slowly erodes, rather than a solid amorphous dispersion as required by the present invention. That is, Sikorski discloses a physical mixture of drug particles and polymer particles but not a solid amorphous dispersion of drug and polymer. For solid amorphous dispersions, each particle comprises both drug and polymer.

6. One of the key features of a solid amorphous dispersion is that it is capable of achieving higher concentrations of dissolved drug in an aqueous use environment relative to crystalline drug or relative to a physical mixture of crystalline drug particles and polymer particles or even a physical mixture of amorphous drug particles and polymer particles. This is demonstrated by the patent examples. Turning to Example 17 at pages 123-128, a solid amorphous dispersion of the present invention consisting of 10 wt% Drug 2:90 wt% HPMC (the dispersion of Example 14) was tested *in vitro*. Table 9 reports dissolved drug concentration for the solid amorphous dispersion of Example 14. For convenience, the results are reproduced in Exhibit 1 attached to this declaration.

7. Similar dissolution tests were performed using (1) a physical mixture of crystalline drug and HPMC (Control A), (2) a physical mixture of amorphous drug and HPMC (Control B), and (3) crystalline Drug 2 alone (Control C). For Control A, a physical mixture containing 10 wt% crystalline Drug 2 and 90 wt% HPMC was prepared by weighing drug and polymer into a container, and mixing the dry powder using a Turbula mixer. For Control B, a physical mixture containing 10 wt% amorphous Drug 2 and 90 wt% HPMC was prepared by weighing drug and polymer into a container, and mixing the dry powder using a Turbula mixer. These physical mixtures, and crystalline Drug 2 alone (Control C), were evaluated in an *in vitro* dissolution test

using the procedures outlined in Example 17 of the instant application. The results of these tests are summarized in Exhibit 1, which also includes the results for the solid amorphous dispersion of Example 14. These data show that the solid amorphous dispersion of Example 14 provided maximum drug concentrations more than a 100-fold that of crystalline drug alone (Control C), while the physical mixtures (Controls A and B) did not provide concentration enhancement relative to crystalline drug alone.

8. In addition, a compressed tablet was formed with drug and HPMC corresponding to the controlled-release formulation or "dispersion" of Sikorski and dissolution tested. One set of tablets was made containing a physical mixture of crystalline Drug 2 and HPMC. A second set of tablets was made containing a physical mixture of amorphous Drug 2 and HPMC. To form the tablets, 1.8 mg crystalline Drug 2, or 1.8 mg of amorphous Drug 2 , was weighed and mixed with 16.2 mg HPMC. Tablets were pressed individually using a Killian press to obtain tablets with a hardness of about 1 kP. An *in vitro* dissolution test was performed to determine the dissolution performance of the tablets of crystalline Drug 2 and HPMC (Control D), and tablets of amorphous Drug 2 and HPMC (Control E). One tablet containing crystalline Drug 2 and HPMC (Control D), and one tablet of amorphous Drug 2 and HPMC (Control E), were each tested in duplicate in PBS using the same procedure as described in paragraph 8 except at a concentration of 1000 μg/mL, if all of the compound had dissolved. Solid amorphous dispersions were also tested at the same total concentration for comparison. The results of this test are summarized in Exhibit 2, which show that the solid amorphous dispersion of the present invention provides concentration-enhancement relative to controlled release formulation tablets containing Drug 2 and HPMC, that is, the "dispersion" of Sikorski. The solid amorphous dispersion of Drug 2 and HPMC provided a maximum drug concentration that was greater than 3360-fold that provided by the tablets of Control D and Control E containing a physical mixture of HPMC and crystalline and amorphous drug, respectively.

9. These data demonstrate that a composition consisting of a physical mixture of 10 wt% crystalline drug and 90 wt% HPMC (corresponding to the "dispersion" composition of Sikorski) has greatly different dissolution characteristics than a solid amorphous dispersion of the present invention consisting of 10 wt% drug and 90 wt% HPMC.

10. These data also demonstrate that a composition consisting of a physical mixture of 10 wt% amorphous drug and 90 wt% HPMC has greatly different dissolution characteristics than

a solid amorphous dispersion of the present invention consisting of 10 wt% drug and 90 wt% HPMC.

11. I further declare that all statements made herein of my own knowledge are true and that all statements made on information are believed to be true; and further that these statements were made with the knowledge that willful false statements and the likes made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Respectfully submitted,

Dwayne T. Friesen

Date: 10/15/2004

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Exhibit 1

Sample	Receptor Solution	Time (min)	Concentration (µg/ml)	AUC (min-µg/ml)
Control A Physical mixture of 10 wt% crystalline Drug 2:HPMC	PBS	0	<0.1	<0.1
		4	<0.1	<0.1
		10	<0.1	<1
		20	<0.1	<2
		40	<0.1	<4
		90	<0.1	<9
		1200	<0.1	<120
Control B Physical mixture of 10 wt% amorphous Drug 2:HPMC	PBS	0	<0.1	<0.1
		4	<0.1	<0.1
		10	<0.1	<1
		20	<0.1	<2
		40	<0.1	<4
		90	<0.1	<9
		1200	<0.1	<120
Control C Crystalline Drug 2 Alone	PBS	0	<0.1	<0.1
		4	0.7	<2
		10	<0.1	<4
		20	<0.1	<5
		40	<0.1	<7
		90	<0.1	<12
		1200	<0.1	<123
Example 14 Solid Amorphous Dispersion of 10 wt% Drug 2:HPMC	PBS	0	0	0
		3	70	106
		10	64	580
		20	59	1,200
		40	50	2,300
		90	42	4,600
		1200	18	37,900

Sample	MDC_{90} (µgA/mL)	AUC_{90} (min*µgA/mL)
Control A Physical mixture of 10 wt% crystalline Drug 2:HPMC	<0.1	<9
Control B Physical mixture of 10 wt% amorphous Drug 2:HPMC	<0.1	<9
Control C Crystalline Drug 2 Alone	0.7	<12
Example 14 Solid Amorphous Dispersion of 10 wt% Drug 2:HPMC	70	4600

Exhibit 2

Sample	Time (min)	Drug 2 Concentration (μgA/mL)	AUC (min*μg/mL)
10% Drug 2:HPMC solid amorphous dispersion (as in Example 14)	0	0	0
	4	336	700
	10	270	2500
	20	252	5100
	40	213	9800
	90	184	19,700
	1200	51	150,300
Tablets of crystalline Drug 2 and HPMC (Control D)	0	<0.1	0
	4	<0.1	<0.1
	10	<0.1	<1
	20	<0.1	<2
	40	<0.1	<4
	90	<0.1	<9
	1200	<0.1	<120
Tablets of amorphous Drug 2 and HPMC (Control E)	0	<0.1	0
	4	<0.1	<0.1
	10	<0.1	<1
	20	<0.1	<2
	40	<0.1	<4
	90	<0.1	<9
	1200	<0.1	<120

Sample	MDC_{90} (μgA/mL)	AUC_{90} (min*μgA/mL)
10% Drug 2:HPMC solid amorphous dispersion (as in Example 14)	336	19,700
Tablets of crystalline Drug 2 and HPMC (Control D)	<0.1	<9
Tablets of amorphous Drug 2 and HPMC (Control E)	<0.1	<9